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| 10/524,977 | 11/28/2005 | Thomas Geoffrey Bird | 100811-1P US | 5876 |

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| EXAMINER | |
|---|---|
| BIANCHI, KRISTIN A | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/524,977 | BIRD ET AL. | |
| | Examiner | Art Unit | |
| | KRISTIN BIANCHI | 4131 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11 and 13-17* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/18/2005 and 08/31/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 11 and 13-17 are currently pending in the instant application. Claims 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected subject matter.

### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on February 18, 2005 and August 31, 2005 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98 and was considered. Signed copies of form 1449 are enclosed herewith.

### ***Response to Restriction***

Applicant's election with traverse of Group I in the reply filed on March 24, 2008 is acknowledged. The traversal is on the ground(s):

"The Examiner is inappropriately using a restriction requirement to limit the scope of claimed embodiment. The proper procedure is to put forward a rejection. We request reconsideration by the Examiner of the restriction between Groups I and II, with reinstatement of Claim 1."

This is not found persuasive because as stated in the lack of unity requirement mailed January 23, 2008, the claims lack unity of invention under PCT rule 13.1 and 13.2 since the technical feature corresponding to the claims, the substituted pyrazole, is not a special technical feature as it fails to define a contribution over the prior art as can be seen by, for example, Cai *et al*. (U.S. Patent No. 6936603) and Dickinson *et al*. (U.S. Patent No. 3277100). Therefore, the claims are not so linked as to form a single general inventive concept and there is a lack of unity of invention because the claims

lack a special technical feature and the technical feature present fails to define a contribution over the prior art. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

The requirement is still deemed proper and is maintained.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of Formula (I) (claim 17) and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for pro-drugs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

***The nature of the invention***

The nature of the invention is the compounds of Formula (I) (claim 17) or salts, **pro-drugs** or solvates thereof, the compound of claim 11, or a salt, **pro-drug** or solvate thereof and a pharmaceutical formulation comprising a compound, or salt, **pro-drug** or solvate thereof, according to claim 1 and a pharmaceutically acceptable diluent or carrier.

***The state of the prior art/level of ordinary skill/level of predictability***

"Pro-drugs" are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized *in vivo* into an active metabolite. Wolff *et al*. (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pages 975-977, 1994) summarizes the state of the prodrug art, the lengthy research involved in successfully identifying a prodrug and the difficulties of extrapolating between species.

The level of skill of the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities as prodrugs. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any prodrug on its face, without evidence to support that particular prodrug.

With the limited direction and exemplification the specification offers, it is highly unpredictable that the compounds of Formula (I) will actually form effective prodrugs thereof. The evidence supports the conclusion that the method of making claimed prodrugs is a subject for further study and experimentation.

***The amount of direction or guidance present/existence of working examples***

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. The specification does not adequately enable a method of making the prodrugs of the compounds that the claims encompass. There is no data or working examples present in the specification for the preparation of prodrugs of the compounds of Formula (I). The instant specification only provides examples of "in-vivo hydrolysable ester forming groups" without disclosing a method for how to add one or more of these to the compounds made to give pro-drugs of the instantly claimed compounds.

***Breadth of the claims***

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include any prodrugs of the claimed compounds.

***The quantity of experimentation needed***

The specification provides limited support, as noted above, for the prodrugs encompassed by the claims. The quantity of experimentation needed to make and use the prodrugs encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would obtain the desired prodrugs in view of the Wolff *et al*. reference.

This discussion established *prima facie* non-enablement. Cancellation of "prodrug" from the claims would overcome this rejection.

Claims 11, 13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of Formula (I) (claim 17) and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

***The nature of the invention***

The nature of the invention is the compounds of Formula (I) (claim 17) or salts, pro-drugs or **solvates** thereof, the compound of claim 11, or a salt, pro-drug or **solvate** thereof and a pharmaceutical formulation comprising a compound, or salt, pro-drug or **solvate** thereof, according to claim 1 and a pharmaceutically acceptable diluent or carrier.

***The state of the prior art/level of ordinary skill/level of predictability***

Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms,

including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. Therefore, for these reasons, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta *et al.*, abstract). In further discussing the predictability of the formation of solvates, Vippagunta *et al.* discloses that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated

into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

***The amount of direction or guidance present/existence of working examples***

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. The specification does not adequately enable a method of making the solvates of the compounds that the claims encompass. There is no data or working examples present in the specification for the preparation of solvates of the compounds of Formula (I). The only direction or guidance present in the instant specification is for the compounds of Formula (I), as well as pharmaceutically acceptable salts and pharmaceutical compositions.

***Breadth of the claims***

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include any solvates of the claimed compounds.

***The quantity of experimentation needed***

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare *any* solvate of the compounds of Formula (I). The science of crystallization has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

This discussion established *prima facie* non-enablement. Cancellation of "solvate" from the claims would overcome this rejection.

## ***Allowable Subject Matter***

The claimed compounds of Formula (I) (claim 17) and pharmaceutically acceptable salts thereof of the instant claims are novel and non-obvious over the prior art because of the structural limitations **M** is $-CH_2-O-$ and $\mathbf{R^8}$ is 1,3-benzodioxol-5-yl. The closest prior art is Walsh *et al*. (WO 00/53602, September 14, 2000). This reference does not encompass the scope of the instant application. Additionally, it does not contain identical or obvious substituents at the aforementioned positions, nor does it contain a substituted pyrazole as its "core structure". A person of ordinary skill in the art would not have expected that making these structurally modifications (to arrive at the instantly claimed compounds) would retain identical activity as disclosed in the prior art.

## ***Conclusions***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIN BIANCHI whose telephone number is (571)270-5232. The examiner can normally be reached on Mon-Fri 7:30-5, alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Janet Andres and Cecilia Tsang can be reached at 571-272-0867 and 571-272-0562, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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